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DK

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/378,528	08/20/99	NABEL	G 8642/72

HM22/0424

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	9

DATE MAILED: 04/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/378,528	Applicant(s) Nabel et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Aug 20, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-28* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-28* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities: The American Type Culture Collection has moved, and the "old" address is found at page 36. Appropriate correction is required.

2. The use of the trademarks WALL STENT, RED KIT O, ANNEXIN-V-FLUOS, FACSCAN and MACLAB 400 have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

3. Claim 16 is objected to because of the following informalities: the claim states "wherein the device is catheter". An "a" should be inserted before "catheter". Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the exemplified cell culture systems and the porcine system, does not reasonably provide enablement for any heme oxygenase gene cell culture system or *in vivo* gene therapy method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to methods for inhibiting vascular smooth muscle cell proliferation and gene therapy comprising contacting a cell with an isolated nucleic acid encoding a heme oxygenase gene. While applicants have shown inhibition of a vascular smooth muscle cell proliferation comprising contacting the cell with an isolated nucleic acid encoding a heme oxygenase gene in certain cell types *in vitro* and in a porcine model system *in vivo*, they have not demonstrated a method for inhibiting vascular smooth muscle cell proliferation comprising contacting the cell with an isolated nucleic acid encoding **any** (emphasis added) heme oxygenase gene *in vitro* or *in vivo*. A method is involving introducing a gene into an animal is gene therapy. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve developing *in vitro* methods other than the exemplified cell culture systems, and a gene therapy method for inhibiting vascular smooth muscle cell proliferation comprising contacting the cell with an isolated nucleic acid encoding a heme oxygenase gene in model systems other than the exemplified porcine system or in an animal subject.

b- A method for expressing a human heme oxygenase gene *in vitro* has been demonstrated in exemplified cell culture systems. A method for expressing a human heme oxygenase gene *in vivo* in a porcine model system has been demonstrated. Limited prophetic guidance on the application of the method to other genes or other model systems or animal subjects has been provided.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and

unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

f- The state of the art as taught by Deremaudt et al. (see especially the abstract, introduction and materials and methods) recite the introduction of a human heme oxygenase gene into a blood vessel endothelial cell model system, where they report an increase in cellular proliferation (angiogenesis). Since the state of the art teaches away from the instant claimed method of inhibition, this demonstrates the unpredictability of the human heme oxygenase gene methods in cell culture and in gene therapy.

g- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

h- The devices claimed in claims 9-28 are all well known medical devices such that said medical devices provide no basis for patentability. The essential element of patentability of all the device claims is the gene encoding human heme oxygenase.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 1 and 8 (and all dependent claims) recite the limitation "functional equivalent". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A "functional equivalent" of a human heme oxygenase gene may be closely patterned after the subject human heme oxygenase gene or may be very loosely patterned after the subject human heme oxygenase gene, such that it may bear no resemblance or form recognizable as the subject human heme oxygenase gene which may be chemically and/or biologically totally unrelated in function or form to the subject human heme oxygenase gene.

9. Claims 1 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms. See MPEP § 2172.01. The omitted step is a correlation, or recapitulation step at the end of the claim which restates the preamble.

10. Claim 3 recites the limitation "expression vector" in line 1. There is insufficient antecedent basis for this limitation in the claim.

11. Claim 6 recites the limitation "expression vector" in line 1. There is insufficient antecedent basis for this limitation in the claim.

12. Claims 10 and 17 appear to claim a Markush group without the proper use of the Markush format. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B ***and*** C." See Ex parte Markush , 1925 C.D. 126 (Comm'r Pat. 1925).

13. Claim 18 recites the limitation "the device" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. in view of Morita et al. and Ali et al.

Lee et al. taught (see especially the abstract, introduction, materials and methods and discussion) a method of inhibiting smooth muscle cell proliferation by tranfecting a smooth muscle cell with a human heme oxygenase gene in a liposome.

Lee et al. did not teach that the gene was in a adenoviral vector.

Morita et al. taught that proliferation of smooth muscle cells in culture were inhibited by human heme oxygenase gene expression.

Ali et al. taught the equivalence of the obvious choices of vectors for practicing a method of gene introduction into a cell, especially the viral vectors including adenoviral vectors.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant claimed invention to combine the method of inhibiting smooth muscle cell proliferation by tranfecting a human smooth muscle cell with a human heme oxygenase gene in a liposome of Lee et al. with the method of inhibiting smooth muscle cell proliferation of Morita et al. and the adenoviral vector of Ali et al. because the teachings of Morita et al. demonstrated that a human heme oxygenase gene expressed in a human smooth muscle cell would inhibit cell proliferation. Ali et al. merely taught the well known use of various viral and non-viral vectors, and the advantages and disadvantages of using them.

One of ordinary skill in the art would have been motivated at the time of filing of the instant claimed invention to combine the method of inhibiting smooth muscle cell proliferation by tranfecting a human smooth muscle cell with a human heme oxygenase gene in a liposome of Lee et al., where it states in the abstract "[c]ells that overexpress HO-1 (A549-A4) exhibited a

marked decrease in cell growth compared to wild type" with the method of inhibiting smooth muscle cell proliferation of Morita et al. where it states in the abstract "CO is produced in vascular smooth muscle cells (VSMC) by heme oxygenase-1 (HO-1)...The inhibition of ET-1 and PDGF-B mRNA by CO resulted in decreased production of these endothelial-derived mitogens, and in turn, inhibition of VSMC proliferation" because the teachings of Morita et al. merely provide an inherent condition of the expression of the human heme oxygenase gene in human smooth muscle cells. Ali et al. merely taught the well known use of various viral and non-viral vectors, and the advantages and disadvantages of using them. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Lee et al. with Morita et al. and Ali et al.

Conclusion

16. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.

Examiner

April 20, 2000

DAVID GUZO
PRIMARY EXAMINER